REMARKS

Claims 1 and 15-28 are currently pending in this application. Claims 1 and 15-28 stand rejected on arguments laid out in the Final Office Action mailed on November 21, 2006. Claims 1 and 15 have been amended. Claims 21 and 26-28 have been canceled by the present amendment. No new claims have been added.

Applicant would first like to thank Examiner Chen for taking time to discuss the outstanding rejections with Applicant's representatives and a Declarant (Dr. Alison O'Neill) during an in-person interview on August 27, 2007. In particular, the topic of enablement for a method of treatment versus enablement for a method of delivery by chlorotoxin was discussed. The Examiner indicated that his concern was that sufficient evidence of successful treatment had not been provided in order to enable a claim to such treatment, and offered that an amendment reciting "delivery" rather than "treatment" would be helpful.

Claim 1 has now been amended to remove references to "treatment" and instead recite a method of "delivering" a cytotoxic moiety such that the agent binds specifically to the tumor. Support for these amendments can be found throughout the Examples section of the specification as originally filed. For example, Example 2 (page 30) shows a summary of data showing that chlorotoxin fused to a detectable biotin group bound selectively to cells associated with tumors and bound up to 95% positive cells per tumor in over 250 human glioma samples, indicating that the moiety fused to chlorotoxin was successfully delivered to tumors and bound specifically to the tumors. Table 1 (page 42) is discussed in Example 17 (page 43) and summarizes the data showing binding of chlorotoxin to neuroectodermally derived tumors. Examples of cytotoxic moieties that can be linked to chlorotoxin can be found on page 27, lines 17-19 of the specification.

Claim 15 has been amended to correct an inadvertent typographical error in the spelling of the word "saporin." Support for the correct spelling of "saporin" can be found in the specification as originally filed on page 30, line17.

Therefore, Applicant submits that no new matter is introduced by these amendments.

In light of the new patent rules that go into effect on November 1, 2007, Applicant would like to take the opportunity to clarify the relationships among the present application and priority applications that were filed *before* implementation of the new patent rules. These new rules

change the permitted characterization of related patent applications, in particular by limiting "divisional" applications to those that were filed in response to a Restriction Requirement.

The present case has been (and, in light of the new amendment, will continue to be) labeled a "divisional" of prior-filed application 09/296,031, which itself was a continuation-in-part of 08/774,154. It is Applicant's belief that the present application is indeed a "divisional" of the recited prior application in that it claims a patentably distinct invention. However, in light of the changed rules and their import, Applicant respectfully requests Examiner's acknowledgement that (1) the present application has a claim set directed to a patentably distinct invention; and (2) the "divisional" status of the present case is correct.

For the convenience of the Examiner, Applicant has enclosed a chart that summarizes the relationships between the aforementioned applications and all other related applications (enclosed as **Appendix A**) and a listing of all the issued and pending claims in the applications in the aforementioned Patent tree (enclosed as **Appendix B**).

As can be seen by reference to the tree, a Restriction Requirement was issued in the "Parent" case dividing the claims into four Groups:

I. Ligands

II. Method of detection

III. Fusion proteins

IV. Method of treating

Claims within Group II were pursued in that Parent case, and three divisionals were filed, with claims within Groups I, III, and IV; each of these cases has now issued. A CIP (also now issued) was also filed with claims within Group II. The present case was filed as a DIV of that CIP.

Given that the present case has included "methods of treating" claims, it is also technically within Group IV. However, Applicant respectfully submits that the currently pending claims, as presently amended, differ from the claims in the only other case that had claims within Group IV, which other case has now issued as U.S. Patent No. 6,319,891. The issued claims in U.S. Patent No. 6,319,891 are directed to a method of treating a tumor expressing a glioma chloride channel, whereas the claims of the present case relate to tumors of neuroectodermal origin. Furthermore, as mentioned above, the present Amendment removes references to method of treatment. The amended claims in the present application now cite

methods of delivering a cytotoxic moiety using chlorotoxin. Applicant therefore submits that the present case is a proper Divisional application, whether the old or new rules are applied. Applicant requests that the Examiner confirm or refute this position in the next Action.

Applicant respectfully requests reexamination and reconsideration of the case, as amended. The current amendments to the claims obviate the rejections levied in the Office Action mailed on November 21, 2006. Nevertheless, each of the rejections levied in the Office Action is addressed below.

Double patenting:

Applicant has been advised in the Office Action that claim 28 will be objected to under 37 CFR § 1.75 as being a substantial duplicate of claim 22 should claim 22 be found allowable; claim 26 and 27 will be objected to under 37 CFR §1.75 as being a substantial duplicate of claim 1 should claim 1 be found allowable; and claim 21 would be objected to under 37 C.F.R. §1.75 as being a substantial duplicate of claim 20 should claim 20 be allowable.

Claims 21, and 26-28 have been cancelled by the present amendment, thus rendering this objection moot. Applicant hereby requests removal of this objection.

Claim rejections under 35 U.S.C. § 112:

Claims 1 and 15-28 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In particular, the Office Action takes the position that "the specification fails to provide adequate guidance and evidence for how to treat various neuroectodermal tumors in the brain by using a pharmaceutical composition comprising a chlorotoxin fused to any cytotoxic moiety *via* various administration routes so as to provide a therapeutic effect *in vivo*." This topic was discussed during the in-person interview of August 27, 2007. Applicant understands the issue raised by the Examiner to be a distinction between enablement for a method of treatment of neuroectodermal tumors and enablement for a method of delivering a cytotoxic moiety to neuroectodermal tumors using chlorotoxin.

In order to advance prosecution of the present case, Applicant has amended independent claim 1 such that it no longer recites a method of treatment. Instead, claim 1 now recites a method of delivering a cytotoxic moiety to neuroectodermal tumors. Claims 15-20 and 22-25 (through their dependence on claim 1) no longer make reference to a method of treatment. Thus, the present amendments render this rejection moot. Applicant hereby requests that the rejection be withdrawn.

CONCLUSION

Applicant again thanks the Examiner for his careful review of the case. The claims have been amended to obviate all rejections. Based on the Remarks presented above, Applicant respectfully submits that Claims 1, 15-20, and 22-25 are now in condition for allowance. A Notice to this effect is respectfully requested.

Please charge any fees that may be associated with this matter, or credit any overpayments, to our Deposit Account No.: 03-1721.

Respectfully submitted,

____/BHJarrell/_____

Dated: October 31, 2007

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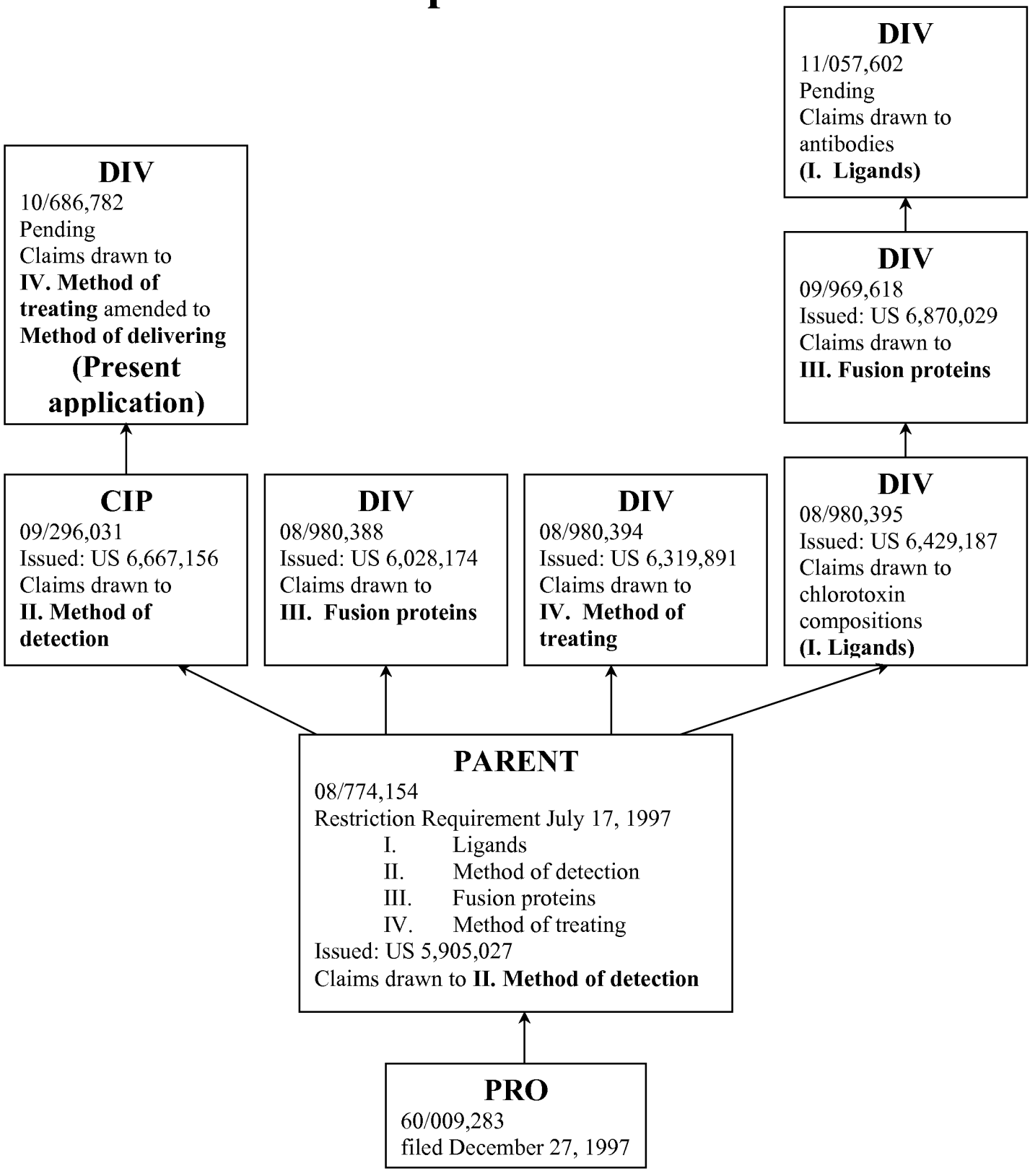
Appendix A

60/009,283
patent tree



Appendix B

Claims in 60/009,283 Patent Tree

Please refer to the enclosed diagram (entitled 60/009,283 patent tree) for a schematic of the relationships between the following patents and applications.

PARENT 08/774,154
Issued: US 5,905,027

1. A method of differentiating glial-derived or meningioma-derived neoplastic tumor tissue from non-neoplastic tissue, comprising the steps of:

contacting a tissue of interest with an antibody that specifically recognizes an antigen specific to chloride channels of glial- or meningioma-derived tumor cells; and

measuring the level of binding of the antibody, wherein an elevated level of binding, relative to normal tissue, is indicative that the tissue is neoplastic.

2. The method of claim 1, wherein said level of antibody binding indicative of neoplastic tissue is from about 30% to about 90% of cells positively binding the antibody.

3. A method of differentiating glial-derived or meningioma-derived neoplastic tumor tissue from non-neoplastic tissue, comprising the steps of:

contacting a tissue of interest with labeled chlorotoxin which binds specifically to glial or meningioma-derived neoplastic tumor tissue; and

measuring the level of binding of the labeled chlorotoxin, wherein an elevated level of binding, relative to normal tissue, is indicative that the tissue is neoplastic.

4. The method of claim 3, wherein said chlorotoxin is selected from the group consisting of native, synthetic and recombinant chlorotoxin.

5. The method of claim 3, wherein said labeled chlorotoxin is radiolabelded and the level of radiolabeled chlorotoxin binding affinity indicative of neoplastic tissue is from about 5 nM to about 5 micromolar.

6. The method of claim 5, wherein said radiolabeled chlorotoxin is selected from the group consisting of .sup.131 I-chlorotoxin and .sup.125 I-chlorotoxin.

7. The method of claim 3, wherein said chlorotoxin is labeled with a fluorescent moiety.

8. The method of claim 7, wherein said fluorescently labeled chlorotoxin binding

is determined by a method selected from the group consisting of fluoresecent microscopy and fluorescent activated cell sorting.

9. The method of claim 6, wherein said labeled chlorotoxin binding is determined using positron emission tomography scanning.

DIV 08/980,388
Issued: US 6,028,174

1. A fusion protein, said protein comprised of a chlorotoxin protein that specifically recognizes an antigen in chloride channels of glial-derived tumor fused to a cytotoxic moiety, wherein the chlorotoxin is selected from a group consisting of native chlorotoxin, synthetic chlorotoxin and recombinant chlorotoxin.

2. The fusion protein of claim 1, wherein said ligand is an antibody.

3. The fusion protein of claim 1, wherein said cytotoxic moieties is selected from the group consisting of gelonin, ricin, saponin, pseudonomas exotoxin, pokeweed antiviral protein, diphtheria toxin, and complement proteins.

DIV 08/980,394
Issued: US 6,319,891

1. A method of treating a tumor expressing a glioma chloride channel in a patient comprising administering an effective amount of a pharmaceutical composition comprising chlorotoxin linked to a cytoxic agent.

2. The method of claim 1 wherein the tumor is glial in origin.

3. The method of claim 2 wherein the tumor is a glioma.

4. The method of claim 3 wherein the glioma is selected from the group consisting of astrocytoma, glioblastoma and medulloblastoma.

5. The method of claim 1 wherein the tumor is meningeal in origin.

6. The method of claim 5 wherein the tumor is a meningioma.

7. The method of claim 1 wherein the cytotoxic agent is selected from the group consisting of gelonin, ricin, saponin, pseudomonas exotoxin, pokeweed antiviral protein, diphtheria toxin and complement proteins.

8. A method of treating a tumor expressing a glioma chloride channel in a patient comprising administering an effective amount of a pharmaceutical composition comprising chlorotoxin fused to a second protein.

9. The method of claim 8 wherein the tumor is meningeal in origin.

10. The method of claim 9 wherein the tumor is a glioma.

11. The method of claim 10 wherein the glioma is selected from the group consisting of astrocytoma, glioblastoma and medulloblastoma.

12. The method of claim 8 wherein the tumor is meningeal in origin.

13. The method of claim 12 wherein the tumor is a meningioma.

14. The method of claim 8 further comprising the step of administering an agent which binds to the second protein.

15. The method of claim 14 wherein the agent is an antibody.

16. The method of claim 15 wherein the second protein is glutathione-S-transferase and the antibody binds to glutathione-S-transferase.

17. The method of claim 15 wherein the antibody is monclonal.

18. The method of claim 14 wherein the agent is linked to a cytotoxic agent.

19. The method of claim 18 wherein the cytotoxic agent is selected from the group consisting of gelonin, ricin, saponin, pseudomonas exotoxin, pokeweed antiviral protein, diphtheria toxin and complement proteins.

20. The method of claim 8 wherein the chlorotoxin is labeled.

21. The method of claim 20 wherein the chlorotoxin label is a radiolabel.

22. The method of claim 21 wherein the chlorotoxin radiolabel is selected from the group consisting of .sup.131 I and .sup.125 I.

23. A method of treating a glioma in a patient comprising administering an effective amount of a pharmaceutical composition comprising chlorotoxin linked to a cytotoxic agent.

24. A method of treating a meningioma in a patient comprising administering an effective amount of a pharmaceutical composition comprising chlorotoxin linked to a cytotoxic agent.

25. A method of treating a glioma in a patient comprising administering an effective amount of a pharmaceutical composition comprising chlorotoxin fused to a second protein.

26. A method of treating a meningioma in a patient comprising administering an effective amount of a pharmaceutical composition comprising chlorotoxin fused to a second protein.

27. The method of any one of claims 23 or 25 wherein the glioma is selected from the group consisting of astrocytoma, glioblastoma and medulloblastoma.

28. The method of any one of claims 23 or 24 wherein the cytotoxic agent is selected from the group consisting of gelonin, ricin, saponin, pseudomonas exotoxin, pokeweed antiviral protein, diphtheria toxin and complement proteins.

29. The method of any one of claims 25 or 26 further comprising the step of administering an agent which binds to the second protein.

30. The method of claim 29 wherein the agent is an antibody.

31. The method of claim 30 wherein the second protein is glutathione-S-transferase and the antibody binds to glutathione-S-transferase.

32. The method of claim 30 wherein the antibody is monoclonal.

33. The method of claim 30 wherein the agent is linked to a cytotoxic agent.

34. The method of any one of claims 1-6, 23 or 24 wherein the cytotoxic agent is a radiolabel.

35. The method of claim 34 wherein the radiolabel is selected from the group consisting of ^{131}I and ^{125}I.

DIV 08/980,395
Issued: US 6,429,187

1. A pharmaceutical composition comprising chlorotoxin wherein the pharmaceutical composition is suitable for use in humans.

2. The composition of claim 1 wherein the chlorotoxin is selected from the group consisting of recombinant chlorotoxin, synthetic chlorotoxin and native chlorotoxin.

3. The composition of claim 1 wherein the chlorotoxin is recombinant chlorotoxin.

4. The composition of claim 1 wherein the chlorotoxin is labeled.

5. The composition of claim 4 wherein the chlorotoxin label is a radiolabel.

6. The composition of claim 5 wherein the chlorotoxin radiolabel is selected from the group consisting of ^{131}I and ^{125}I.

7. The composition of claim 4 wherein the chlorotoxin label is a fluorescent moiety.

8. A pharmaceutical composition comprising a pharmacologically effective dose of chlorotoxin and a cytotoxic moiety that is effective to treat an individual having a glioma or meningioma.

9. A pharmaceutical composition comprising a pharmacologically effective dose of chlorotoxin and a cytotoxic moiety that is effective to suppress the growth of tumor cells which are glial in origin.

CIP 09/296,031
Issued: US 6,667,156

1. A method of detecting a neuroectodermal tumor in a patient comprising: (a) adding chlorotoxin to a patient tissue sample; and (b) detecting the binding of chlorotoxin to the tissue sample wherein an elevated level of binding relative to normal tissue is indicative of the presence of the neuroectodermal tumor.

2. The method of claim 1 wherein the neuroectodermal tumor is selected from the group consisting of glioma, meningioma, ependymonas, medulloblastoma, neuroblastoma, glioblastoma, ganglioma, pheochromocytoma, melanoma, Ewing's sarcoma, small cell lung carcinoma and metastatic brain tumors.

3. The method of claim 1 wherein the chlorotoxin is labeled.

4. The method of claim 3 wherein the chlorotoxin label is detected by enzyme-linked immunosorbent assay.

5. The method of claim 3 wherein the chlorotoxin label is a radiolabel.

6. The method of claim 5 wherein the radiolabel is selected from the group consisting of ^{3}H, ^{14}C, ^{32}P, ^{35}S, ^{36}Cl, ^{51}Cr, ^{57}Co, ^{58}Co, ^{59}Fe, ^{90}Y, ^{186}Re, ^{131}I and ^{125}I.

7. The method of any one of claims 5 or 6 wherein the radiolabel is detected by positron emission tomography scanning.

8. The method of claim 3 wherein the chlorotoxin label is a fluorescent moiety.

9. The method of claim 8 wherein the fluorescent moiety is selected from the group consisting of fluorescein, rhodamine, auramine, Texas Red, AMCA blue and Lucifer Yellow.

10. The method according to claim 8 wherein the fluorescent moiety is detected by a method selected from the group consisting of fluorescent microscopy and fluorescent activated cell sorting.

11. The method of claim 3 wherein the chlorotoxin label is biotin.

12. The method of claim 11 further comprising the step of contacting the sample with avidin to form avidin-biotin-labeled chlorotoxin complexes.

13. The method of claim 12 further comprising the step of contacting the avidin-biotin-labeled chlorotoxin complexes with 3'3'-diaminobenzidine to form a colormetric product wherein the level of the colormetric product is indicative of the level of chlorotoxin binding.

14. The method of claim 3 wherein the detecting of the binding of chlorotoxin to the tissue sample comprises measuring the binding of chlorotoxin to the tissue sample.

15. The method of claim 1 wherein the tissue sample is frozen.

16. The method of claim 1 wherein the tissue sample is embedded in paraffin.

17. The method of any one of claims 15 or 16 wherein the tissue sample is counterstained.

18. The method of claim 17 wherein the counterstain is selected from the group consisting of methyl green, hematoxylin and eosin.

DIV 09/969,618
Issued: US 6,870,029

1. A fusion protein comprising chlorotoxin fused to a second protein.

2. The fusion protein of claim 1 wherein the second protein is glutathione-S-transferase.

3. The fusion protein of claim 1 wherein the second protein is a cytotoxic moiety.

4. The fusion protein of claim 3 wherein the cytotoxic moiety is selected from the group consisting of gelonin, ricin, saponin, pseudomonas exotoxin, pokeweed antiviral protein, diphtheria toxin and complement proteins.

5. The fusion protein of claim 1 wherein the chlorotoxin consists of thirty-six amino acids.

6. The fusion protein of claim 1 wherein chlorotoxin is separated from the second protein by a linker peptide wherein the linker peptide consists of 10 or 20 alanine residues.

7. The fusion protein of claim 1 wherein the fusion protein is labeled.

8. The fusion protein of claim 7 wherein the label is a radiolabel.

9. The fusion protein of claim 8 wherein the radiolabel is selected from the group consisting of ^{131}I and ^{125}I.

DIV 10/686,782
Pending
Currently pending claims (includes Amendment filed on October 31, 2007):

1. A method of delivering a cytotoxic moiety to a neuroectodermal tumor, comprising: administering a pharmaceutical composition comprising an effective dose of an agent consisting of chlorotoxin fused to a cytotoxic moiety to an individual having a neuroectodermal tumor, such that the agent binds specifically to the tumor.

2-14. **Cancelled**

15. The method of claim 1 wherein the chlorotoxin is fused to a cytotoxic moiety selected from the group consisting of gelonin, ricin, saporin, pseudomonas exotoxin, pokeweed antiviral protein, diphtheria toxin, and complement proteins.

16. The method of claim 1, wherein the neuroectodermal tumor is a tumor type treated is selected from the group consisting of ependymonas, medulloblastomas, neuroblastomas, gangliomas, pheochromocytomas, melanomas, peripheral primitive neuroectodermal tumors, small cell carcinoma of the lung, Ewing's sarcoma, and metastatic tumors in the brain.

17. The method of claim 15, wherein the chlorotoxin is selected from the group consisting of native chlorotoxin, synthetic chlorotoxin and recombinant chlorotoxin.

18. The method of claim 17, wherein the neuroectodermal tumor is a glioma.

19. The method of claim 18, wherein the glioma is selected from the group consisting of WHO grade IV: glioblastoma multiforms, WHO grade III: anaplastic astrocytoma, WHO grade II: low grade, WHO grade I: pliocytic astrocytoma, oligodendrogliomas, gangliomas, meningiomas and ependymomas.

20. The method of claim 17, wherein the tumor is selected from selected from the group consisting of ependymonas, medulloblastomas, neuroblastomas, gangliomas, pheochromocytomas, melanomas, peripheral primitive

neuroectodermal tumors, small cell carcinoma of the lung, Ewing's sarcoma, and metastatic tumors in the brain.

21. **(Canceled)**

22. The method of claim 1 wherein the composition further comprises a pharmaceutically acceptable carrier.

23. The method of claim 1 wherein the composition is suitable for parenteral administration.

24. The method of claim 1 wherein the parenteral administration is selected from the group consisting of intravenous, intramuscular, intrathecal and subcutaneous administration.

25. The method of claim 1 wherein the dose of chlorotoxin is effective to reduce the size of the tumor.

26-28. **(Canceled)**

DIV 11/057,602
Pending
Currently pending claims (includes Amendment filed on October 31, 2007):

1. A pharmaceutical composition, which composition comprises:

a monoclonal antibody that specifically binds to a site on tumor cells of glial or meningial origin, which site is characterized that, when such tumor cells, absent the antibody, are contacted with chlorotoxin, chlorotoxin binds to the site; and

a pharmaceutical acceptable carrier.

2. The pharmaceutical composition of claim 1, wherein the monoclonal antibody is fused to a cytotoxic moiety.

3. The pharmaceutical composition of claim 2, wherein the cytotoxic moiety is selected from the group consisting of gelonin, ricin, saponin, pseudonomas, exotoxin, pokeweed antiviral protein, diphtheria toxin, and complement proteins.

4. The pharmaceutical composition of claim 1, wherein the monoclonal antibody does not bind to tumors of non-glial or meningiomal origin.